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Comparison of Clinical Efficacy of Topical Pimecrolimus with Betamethasone in Chronic Skin Lesions Due to Sulfur Mustard Exposure: A Randomized, Investigator-Blind Study

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Abstract: This study compared topical pimecrolimus with betamethasone in the treatment of pruritus and chronic skin lesions due to sulfur mustard exposure. Seventy male chemical-injured war veterans participated in this investigator-blinded clinical trial. They were randomized to receive pimecrolimus cream 1% (n = 35) or betamethasone cream 0.1% (n = 35) two times a day for 6 weeks. Dermatological examination and assessment of pruritus severity by a pruritic score questionnaire and visual analogue scale were done before and after the treatment course. A significant decrease ($P < 0.05$) in pruritus, burning sensation, and skin dryness was shown in both groups after the treatment. However, the severity of hyper- and hypopigmentation, vesicle, erythema, fissure, lichenification and excoriation did not decrease significantly in either group ($P > 0.05$). Mean (± standard deviation) pruritic scores at baseline for the pimecrolimus and betamethasone groups were 30.4 (± 8.0) and 33.6 (± 7.2), respectively ($P = 0.103$). These scores decreased to 18.8 (± 4.8) in the pimecrolimus and 20.8 (± 4.0) in the betamethasone groups after treatment; both showed a statistically significant decrease ($P < 0.001$). Change of pruritus score from baseline to after the treatment course was not statistically different between the two groups ($P = 0.502$). No serious side-effects were reported during the course of the treatment. Topical pimecrolimus 1% was as effective as betamethasone cream 0.1% in controlling pruritus, burning sensation and skin dryness of sulfur mustard-exposed patients.

Sulfur mustard (bis-2-chloroethyl sulfide; HD) is an agent with potent mutagenic, carcinogenic, cytotoxic and vesicant properties [1]. The organs most commonly affected are the skin, eyes and respiratory system [2,3]. This agent was used extensively as a vesicant chemical warfare agent during the Iraq–Iran War (1983–88) [4].

The skin is one of the first organs to be exposed to mustard gas. When delivered as liquid or vapour, sulfur mustard easily penetrates the skin; therefore, the skin (because of its high surface area compared to other organs) suffers the most damage [5]. Skin involvement in mustard gas exposure can be divided into two categories; namely, acute and chronic. Chronic skin complications of sulfur mustard have been reported in previously published papers [6–8]. Pruritus has been reported to be the most common complaint in 70–90% of sulfur mustard-exposed patients who suffered from chronic skin lesions. Following pruritus, burning sensation, pain and redness were the most common symptoms, respectively. In physical examination, xerosis (dry skin) was the most common finding, followed by hyperpigmentation, hypopigmentation and scarring [9].

Treatment of skin lesions and pruritus in the chronic phase is mainly symptomatic [10]. Oral antihistamines, local moisturizers and, particularly, topical corticosteroids such as betamethasone are currently the most administered medications for skin lesions in our dermatology clinics. However, long-term application of topical corticosteroids has been reported to be accompanied by adverse effects, such as skin atrophy, striae, rosacea, acne, etc. [11,12].

Pimecrolimus (32-epi-chloro-32-desoxyascomycin, SDZ ASM 981) is a derivative of macrolactam ascomycin. It is an immunosuppressive agent that works by inhibiting calcineurin in the skin, which regulates the activity of several transcription factors that control cell division and trigger the early stages of T-cell activation [13]. Several clinical trials have shown pimecrolimus cream 1% to be effective in resolving the signs and symptoms of both atopic and non-atopic dermatitis [14–16]. However, its efficacy in controlling the symptoms of sulfur mustard-exposed patients who suffer from chronic skin lesions and, more importantly, pruritus has not been evaluated yet. The purpose of this trial was to compare the effect of topical pimecrolimus cream 1% with betamethasone cream 0.1% in the treatment of the chronic skin lesions and pruritus of these patients.

Materials and Methods

The study was designed as an investigator-blinded randomized clinical trial, conducted from July to December 2006 in the outpatient dermatology clinic of Baqiyatallah Hospital, Tehran, Iran. This hospital provides tertiary medical care and maintains a large number of medical records of patients exposed to mustard gas during the Iraq–Iran War. Inclusion criteria were the following: males age 30–65 years, exposed to sulfur mustard, and suffering

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from chronic pruritic skin lesions. The exposure was confirmed from related medical documents, which included development of blisters in the exposed areas of the skin and transient visual deterioration lasting for several days and associated respiratory symptoms. Patients were excluded if itching resulted from systemic or cutaneous non-chemical diseases, or if they had received any topical treatments within 1 month prior to the study.

A consecutive sampling method was used to select eligible patients. The patients were allocated into two groups (A and B) based on a randomization protocol made by computer-generated random number that sequenced blocks AB and BA. Patients in group A received pimecrolimus cream 1% (Elidel®, Novartis AG, Basel, Switzerland) and patients in group B received betamethasone cream 0.1% (Aburaihan Pharmaceutical Co., Tehran, Iran) twice daily for 6 weeks. In order to determine the effective drug amount, we used Finger Tip Unit which is the amount of ointment expressed from a tube with a 5-mm diameter nozzle, applied from the distal skin-crease to the tip of the index finger. This amount nearly equals 0.47 g in males, and one Finger Tip Unit is enough to cover both sides of a hand from the wrist to finger tips [17]. The first application was made at the outpatient clinic under supervision to determine any hypersensitivity reactions.

For assessment of pruritus severity, a visual analogue scale (VAS), designed as a 100-mm horizontal line without scaling (0 = no pruritus to 100 = unbearable pruritus), was applied. In addition, a pruritic score questionnaire was calculated according to the questionnaire before and after the treatment course for each patient [18]. The entire 24-hr period was divided into three periods: morning, the time from getting up until noon; afternoon, the time from noon until going to bed; and night. We allotted 1 point for report of pruritus in each period, to a maximum of 3 points for a patient who complained of pruritus during all three periods. The scores of severity, distribution and frequency of pruritus were recorded separately for the morning and the afternoon; sleep duration and waking up were also recorded at night (table 1). The pruritus score ranges from 1 to 48, with a higher score indicating more severe pruritus. This range is divided into three equal sections as mild (1–16 points), moderate (17–32 points) and severe (33–48 points).

Patients were visited by a board-certified dermatologist at baseline and at the end of treatment duration. Observed skin disorders (hyper- and hypopigmentation, vesicle, scaling, dry skin, erythema, fissure, lichenification and excoriation) and the patients' symptoms (pruritus and dry skin) were entered to a checklist. To ensure that the dermatologist remained blinded to treatment allocation throughout the study, he was not permitted to see the medications.

Patients could not be blinded to treatment because of the obvious differences in the colour, smell and consistency of the two medications studied.

Table 1.

Pruritus score.

	Morning	Afternoon	Night	Total
Period	1	1	1	3
Severity	5	5		10
Distribution	5	5		10
Frequency	5	5		10
Sleeping			10	10
Waking up			5	5
Total	16	16	16	48

Points were awarded for: *Severity*: Itching without need to scratch (1 point); itching with occasional need to scratch (2 points); frequent scratching (3 points); no itching relief with scratching (4 points); itching with discomfort all the time (5 points). *Distribution*: For each body part: arms, trunk or legs (1 point); generalized itching (5 points). *Frequency*: Itching in two periods of less that 10 min. or one period of more than 10 min. (1 point); itching in ten periods of less than 10 min. or five periods of more than 10 min. (5 points). *Sleeping*: Absence of sleep (10 points); 7 hr or more of night sleep (0 points). Other points were scored by the deduction of the number of sleeping hours from that of 10. *Waking up*: For each time of waking up due to pruritus (1 point); maximum of 5 points for five or more episodes.

Statistical analyses. Descriptive indices like frequency, percentage, mean and standard deviation (S.D.) were used to express data. Difference of pruritus severity and its change from baseline to after the treatment (according to VAS and pruritic score) were tested by the independent sample t-test. Comparison of changes in these two measures before and after the treatment period was performed by paired sample t-test. The chi-squared test was used for categorical variables (presentation of skin lesions and involved anatomic regions). Comparison of proportion of patients that their pruritus improved according to pruritus score categories (mild, moderate, and severe) was also performed by the chi-squared test. P values < 0.050 selected as a significant level. All statistical analyses were done by SPSS software for Windows (version 13) (SPSS Inc., Chicago, IL, USA). The study protocol was in conformity with the ethical guidelines of the 1975 Declaration of Helsinki [19].

Results

A total of 70 male patients were randomized into two groups: 35 patients in the pimecrolimus group and 35 patients in the betamethasone group. Thirty-two patients completed the study in each group. Six patients (three in each group) could not be contacted and were dropped from the trial. The mean (± S.D.) ages of patients in the pimecrolimus and betamethasone groups were 44.2 (± 7.7) and 46.1 (± 6.0) years, respectively ($P = 0.273$). All the patients had been exposed to at least a single high dose of sulfur mustard as a chemical warfare agent, on an average 19 years ago (from 1982 to 1987). No significant difference was observed with regard to the mean time of exposure between pimecrolimus (19.7 ± 7.8 years ago) and betamethasone group (21 ± 6.3 years ago) ($P = 0.474$).

All patients in both groups complained of pruritus (100%). Distribution of various skin disorders before and after treatment in each group is presented in table 2. As shown, except for scaling, there was no statistically significant difference between the two groups regarding skin disorders either at baseline or after treatment. Both groups showed a significant decrease ($P < 0.05$) in pruritus, burning sensation, and skin dryness following applied treatments. However, the severity of hyper- and hypopigmentation, vesicle, erythema, fissure, lichenification and excoriation did not decrease significantly in either group ($P > 0.05$).

The groin was the most commonly involved region in both the groups. The frequency of itching and eczema locations before and after treatment is shown in table 3.

Mean (± S.D.) visual analogue scale (VAS) scores of pruritus at baseline in the pimecrolimus and betamethasone groups were 45.2 (± 10.3) and 49.9 (± 15.3), respectively ($P = 0.08$) (fig. 1). VAS decreased to 26.7 (± 7.0) in the pimecrolimus group, and to 34.6 (± 11.4) in the betamethasone group after treatment. VAS decreases in both groups were statistically significant ($P < 0.001$). Change of VAS from baseline

Table 2.

Comparison of chronic skin disorders among sulfur mustard-exposed patients who received topical pimecrolimus 1% or betamethasone 0.1% before and after treatment.

	Baseline			After treatment		
	Pimecrolimus	Betamethasone	Significance	Pimecrolimus	Betamethasone	Significance
Pruritus	32 (100)	32 (100)	–	17 (53.1)	12 (37.5)	0.2
Burning sensation	21 (65.6)	22 (68.8)	0.7	10 (31.3)	9 (28.1)	0.7
Hyperpigmentation	11 (34.4)	12 (37.5)	0.7	11 (35.5)	13 (40.6)	0.6
Hypopigmentation	4 (12.5)	6 (18.8)	0.4	4 (12.9)	5 (15.6)	0.7
Vesicle	7 (21.9)	7 (21.9)	0.9	7 (21.9)	7 (21.9)	0.9
Scaling*	13 (40.6)	21 (65.6)	0.04	13 (40.6)	10 (31.3)	0.4
Dry skin	17 (53.1)	23 (71.9)	0.1	8 (25)	8 (25)	0.9
Erythema	9 (28.1)	5 (15.6)	0.2	7 (21.9)	3 (9.4)	0.1
Fissure	6 (18.8)	8 (25)	0.5	2 (6.3)	5 (15.6)	0.2
Lichenification	3 (9.4)	7 (21.9)	0.1	3 (9.4)	7 (21.9)	0.1
Excoriation	6 (18.8)	5 (15.6)	0.7	6 (18.8)	2 (6.3)	0.1

All data are expressed as frequency (percentage); Significance (P value). P values compare the frequency of skin disorders between two studied groups at baseline and after treatment using the chi-squared test.
*Only in the betamethasone group significant decrease was observed after treatment (P = 0.003).

to after the treatment course was not statistically different between two groups (P = 0.227).

Figure 2 depicts mean pruritic scores at baseline and after treatment in both the pimecrolimus and betamethasone groups. Similar to VAS, pruritic scores decreases were significant in both groups (P < 0.001). Change of pruritus score from baseline to after the treatment course was not statistically different between the two groups (P = 0.502).

The pruritus severity of 20 patients (65.2%) in the betamethasone group and 22 cases (68.8%) in the pimecrolimus group improved after treatment (i.e. moved to a less severe category) (P = 0.599). The different severities of pruritus (mild, moderate and severe) in both groups are shown in table 4.

In the pimecrolimus group, 12 patients (37.5%) reported side-effects, as 5 patients complained from hot skin flares, 6 from erythema, and one patient reported burning sensation at the site of application. However, these events were not serious and diminished with continuation of the treatment.

Discussion

Chronic skin inflammation and irritation by sulfur mustard is a complex phenomenon that involves damage to epidermal cells, fibroblasts of dermis, and endothelial cells. Pro-inflammatory cytokines, such as interleukin-1β (IL-1β), IL-8, tumour necrosis factor-α, and IL-6, have been shown to play a major role in the initiation of inflammatory and immunological responses of sulfur mustard injury [20,21]. Due to the chronic nature of induced skin lesions [22], administration of proper topical and/or systemic medications for controlling the inflammation and its related symptoms like pruritus and erythema has a high priority in the clinical management of mustard gas-exposed patients.

Pimecrolimus binds with high affinity to protein receptor macrophilin-12 (FKBP-12) at nanomolar concentrations, and the resulting drug-protein complex inhibits calcium-dependent phosphatase, calcineurin, causing a signal transduction blockade in target cells. As a result, the synthesis of

Table 3.

Distribution of the involved anatomic regions before and after treatment of sulfur mustard-exposed patients who received topical pimecrolimus 1% or betamethasone 0.1%.

	Baseline			After treatment		
	Pimecrolimus	Betamethasone	Significance	Pimecrolimus	Betamethasone	Significance
Head	5 (15.6)	5 (15.6)	0.9	5 (15.6)	4 (12.5)	0.7
Face	7 (21.9)	6 (18.8)	0.7	2 (6.3)	1 (3.1)	0.5
Thorax	22 (68.8)	18 (56.3)	0.3	5 (15.6)	6 (18.8)	0.7
Back	14 (43.8)	15 (46.9)	0.8	6 (18.8)	3 (9.4)	0.2
Upper extremities	18 (56.3)	17 (53.1)	0.8	0	0	0.9
Lower extremities	18 (56.3)	17 (53.1)	0.8	14 (43.8)	8 (25)	0.1
Groin	25 (78.1)	20 (62.5)	0.1	22 (68.8)	16 (50)	0.1
Genitalia and perineum	6 (18.8)	8 (25)	0.5	2 (6.3)	3 (9.4)	0.6
Armpit	14 (43.8)	8 (25)	0.1	4 (12.5)	0	0.03

All data are expressed as frequency (percentage); Significance (P value). P values compare the frequency of involved anatomic regions between the two studied groups at baseline and after treatment using the chi-squared test.

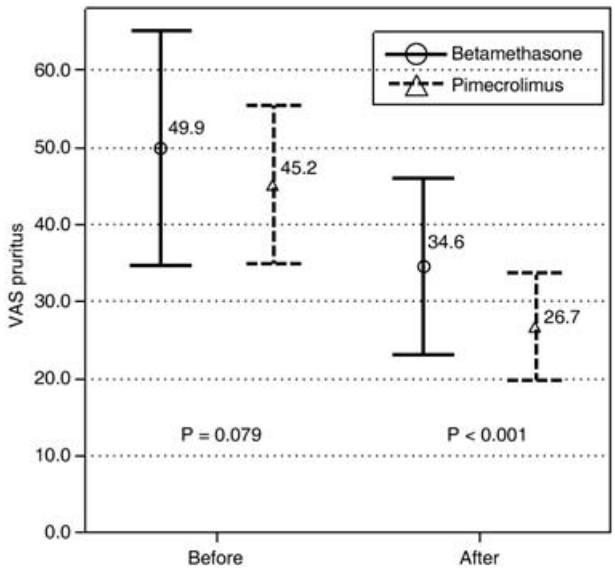

Fig. 1. Mean (standard deviation) visual analogue scale (VAS) score of pruritus in two groups of sulfur mustard-exposed patients who received topical pimecrolimus 1% or betamethasone 0.1%.

inflammatory cytokines from T cells and mast cells is blocked at the level of gene transcription [23]. The current results show that except for the armpit region, pimecrolimus cream 1% had an equal efficacy in comparison to betamethasone cream 0.1% in reducing pruritus, burning sensation and dry skin, particularly in the thorax, back and upper extremities. In the head region, we did not achieve any improvement in either of the groups, which may be related

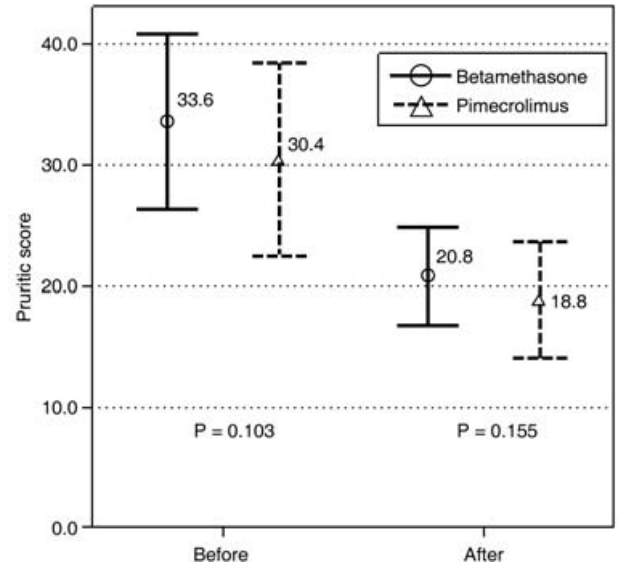

Fig. 2. Mean (standard deviation) pruritus scores of sulfur mustard-exposed patients who received topical pimecrolimus 1% or betamethasone 0.1% before and after treatment.

Table 4.

The pruritus severity at baseline and after the treatment in two studied groups.

Pruritus severity	Pimecrolimus	Betamethasone
Baseline		
Mild	1 (3.1%)	0
Moderate	14 (43.8%)	13 (40.6%)
Severe	17 (53.1%)	19 (59.4%)
After treatment		
Mild	6 (18.8%)	1 (3.1%)
Moderate	26 (81.3%)	30 (93.8%)
Severe	0	1 (3.1%)
Improvement*	22 (68.8%)	20 (62.5%)

*Proportion of patients in whom pruritus severity decreased and they were moved to a less severe category.

to the presence of hair that can decrease the absorption of the administered creams and also the patients' desires for application of the medications. In addition, pruritus severity according to both pruritic score and visual analogue scale was decreased significantly in both groups. Because of the high prevalence of pruritus among these patients (all patients complained of this problem prior to enrolment), this finding is so valuable and not only alleviates this common symptom, but also can increase the quality of life of chemical-injured veterans [24]. The reported side-effects in the pimecrolimus group were not as serious that application was stopped. This is an advantage of topical pimecrolimus in comparison to other systemic medications that have been studied previously in our institute [25,26]. The severity of pruritus significantly decreased in more than 70% of patients receiving systemic hydroxyzine or doxepin; however, sedation was reported among 56% of patients in the doxepin group, and 72% in hydroxyzine group. Dizziness was also reported in two patients in each group [25]. In the Panahi *et al.* study, a phenol 1% and menthol 1% combination showed significant therapeutic effects for pruritus and other chronic skin lesions in comparison to placebo [27]. The prevalence of pruritus decreased from 100% to 85% in the drug group and similar to our results, a significant decrease in scaling and skin dryness was observed after treatment. Because of its minimal atrophogenic effects and percutaneous resorption, pimecrolimus has the advantage over corticosteroids of being safe to use for longer periods and on larger areas of the body [28]. One of the disadvantages of pimecrolimus is the high cost for patients, especially in long-term application. In Iran, the Veterans Organization, which is the official organization for compensation of disabled veterans of war, covers all health-related expenses of sulfur mustard-exposed victims. Therefore, for this specific patient group, the high cost of pimecrolimus would not be a major problem. A limitation we encountered during this study was the low sample size, which can potentially decrease the power of the analyses performed. According to statistical calculations, more than 100 eligible patients were

required in each group for more definite evaluation of equal effectiveness of the topical medications studied. However, recruiting of such a sample was far beyond the time and financial support of this research. In conclusion, pimecrolimus cream 1% was well tolerated and was as effective as topical betamethasone 0.1% in the treatment of the chronic skin lesions and pruritus due to sulfur mustard exposure.

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